

# EFFICACY OF ARTEMETHER-LUMEFANTRINE TREATMENT IN PATIENTS WITH ACUTE UNCOMPLICATED FALCIPARUM MALARIA IN MAYOTTE, A FRENCH COLLECTIVITY OF THE COMOROS ARCHIPELAGO

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## Summary:

Mayotte is a French island located in the Comoros archipelago in the Indian Ocean. Due to the high level of resistance to chloroquine and sulfadoxine-pyrimethamine in this area, new therapeutic strategies are required. The aim was to assess and to document the efficacy of artemether-lumefantrine (AL) combination in four oral dosages. The follow-up was carried out during 21 days to monitor the antimalarial drug efficacy in an open trial in April-May, 2002. Results were obtained from 51 patients, aged from three to 46 years (12 % less than five years). No case of therapeutic failure was observed. At day 2 after treatment, all the patients were afebrile and none of them had parasitaemia until day 21. This first therapeutic trial of the AL combination in the Indian Ocean sub-region shows that this association is safe, effective and rapid. AL should be an alternative treatment of uncomplicated malaria attacks in Comoros Archipelago, and will be of help to manage imported chloroquine-resistant falciparum malaria strains in Madagascar.

**KEY WORDS :** *Plasmodium falciparum*, malaria, chemotherapy, artemether-lumefantrine, Coartem®, Mayotte, France.

**Résumé :** EFFICACITÉ DU TRAITEMENT PAR ARTEMETHER-LUMÉFANTRINE SUR L'ACCÈS PALUSTRE SIMPLE À *PLASMODIUM FALCIPARUM* À MAYOTTE, COLLECTIVITÉ DÉPARTEMENTALE FRANÇAISE DE L'ARCHIPEL DES COMORES

L'île de Mayotte est une collectivité départementale française dans l'archipel des Comores où les résistances parasitologiques à la chloroquine et à la sulfadoxine-pyriméthamine ont atteint un haut niveau, tel qu'une nouvelle stratégie thérapeutique est nécessaire. L'objectif de cette étude, réalisée entre le 22 avril et le 22 mai 2002, a été de documenter l'efficacité de l'artemether-luméfántrine en quatre doses par voie orale au cours d'un suivi post-thérapeutique de 21 jours. Les résultats proviennent de 51 sujets, âgés de 3 à 46 ans (12 % de moins de cinq ans). Aucun échec thérapeutique n'a été enregistré. Au jour 2 après le traitement, tous les patients ont été afebriles et, des jours 2 à 21, présentaient une parasitémie nulle. Ce premier essai thérapeutique de l'artemether-luméfántrine dans la sous-région de l'Océan Indien montre que l'association est bien tolérée, performante et rapidement efficace. Cette association peut constituer une alternative au traitement des accès palustres simples dans l'Archipel des Comores, et pourra aider à contenir l'importation de souches chloroquino-résistantes de *Plasmodium falciparum* à Madagascar.

**MOTS CLÉS :** *Plasmodium falciparum*, paludisme, chimiothérapie, artemether-luméfántrine, Coartem®, Mayotte, France.

An active antimalarial campaign has been running in Mayotte for 25 years. It has been scaled-up over the last five years by: i/ a sustainable antivectorial fight, ii/ the use of dipstick tests and the early treatment of patients, iii/ an epidemiological surveillance system. These actions have reduced the prevalence of malaria to 2 % of the inhabitants (Roussin *et al.*, 2002). It is still difficult to envisage the total eradication of malaria from this Indian Ocean island because the presence of one among the world best vector, *Anopheles gambiae* (Léong Pock Tsy *et al.*,

2003), with high levels of immigration by parasite-carriers from neighboring islands. The Mayotte health and social system provides free public care at all levels. This privilege has attracted numerous immigrants.

As premunition is low in Mayotte Island, both morbidity and mortality due to malaria are a concern for all age groups. The treatment protocol recommended at the beginning of 2002 by the *Direction des Affaires Sanitaires et Sociales* (DASS Mayotte) was chloroquine (CQ) as first line treatment and sulfadoxine-pyrimethamine (SP) as second line. Quinine (Q) was reserved for severe cases. Up till 1988, CQ was completely effective against *Plasmodium falciparum* strains isolated in Mayotte (Julvez & Galtier, 1989). Recent studies have shown that the prevalence of the *pfcr* and *pfdhfr* resistance genes is high in Mayotte (Durand *et al.*, 2001) and in the other islands in the Comoros archipelago (Ariey *et al.*, 2002). Concomitant analysis of medical files in one of the Mayotte's clinics in January 2002

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showed that CQ treatment failed in 70 % (34 malaria attacks considered; unpublished DASS Mayotte's data). In most cases, patients suffered from early treatment failure. Where CQ treatment failed, the initial use of SP as a second line of treatment obtained good results. But the efficiency of SP has been declining in parallel with increasing use, as noticed in Africa and other regions of the world (Krogstad, 1996; White, 1992). This situation has led to the use of a wide variety of drugs to treat uncomplicated malaria on the island. Some clinicians still prescribe CQ first, whereas others prescribe SP, a combination of CQ plus SP or oral quinine (Q). Private doctors usually prescribe halofantrine first.

Thus, in hope to identify a consensual treatment, we designed a prospective cohort study to evaluate the efficacy of the artemether-lumefantrine (AL) for the treatment of uncomplicated *falciparum* malaria in Mayotte. This study reports on the first experience on antimalarial combination therapy in the Comoros Archipelago.

## MATERIAL AND METHODS

This study was carried out from 22 April to 17 May 2002 in Mayotte Island, part of the Comoros Archipelago using the WHO protocol for monitoring the antimalarial drug resistance (WHO 1996). All patients older than two years who attended in the four peripheral health care centers on the island or the outpatient department of Mayotte Hospital were eligible if they met the following criteria: fever (axillary temperature  $\geq 37.5^\circ\text{C}$  and  $< 39.5^\circ\text{C}$ ), acute uncomplicated *P. falciparum* infection diagnosed by a dipstick test based on immunocapture using *Plasmodium* lactate dehydrogenase (Diamed OptiMAL; Diamed AG 1785 Cressier Switzerland) (Piper *et al.*, 1999), and confirmed by a thick blood smear as a *P. falciparum* monospecific infection, living and residing permanently on the island. Breastfeeding, pregnant women and patients with signs or symptoms of severe and complicated malaria as defined by the WHO criteria were excluded (Warrell *et al.*, 1990). Each patient included completed a standardized questionnaire, underwent a basic clinical examination and received paracetamol.

Hour 0 was defined as the time of the first ingested dosage. Patients received Coartem® (Novartis) in four oral dosages ingested at 0 hr, 8 hr, 24 hr, and 48 hr in the presence of a supervisor. One tablet contained 20 mg of artemether and 120 mg of lumefantrine. Each dosage was composed of two tablets for patients of 10-14 kg, four tablets for 15-24 kg, six tablets for 25-34 kg, and eight tablets for  $\geq 35$  kg.

Follow up of patients was performed on days 1, 2, 3, 7, 14 and 21. Patients who failed to attend were traced by a home visitor. Temperature and parasite density were measured at each visit. Blood samples were collected using venipuncture on days 0 and 3 for dosage of hemoglobin and glycemia.

Using finger-prick puncture, blood smears were prepared for parasite counts on days 0, 1, 2, 3, 7, 14, 21. All thick blood smears were Giemsa stained and examined by an experienced microscopist in the following way: 200 oil-immersion microscope fields were counted (about 0.5 ml of blood). The ratio of trophozoites to leukocytes was established by counting the trophozoites until 200 leukocytes had been observed (if the ratio was  $\geq 0.01$ ) or from the total number of trophozoites observed in 200 fields and an estimate of the average number of leukocytes per microscope field (if the ratio was  $< 0.01$ ). Blood films were considered negative if no parasites were seen in 200 oil-immersion fields in a thick blood film. For quality control, 10 % of enrolled patients were randomly selected and their thick blood smears were re-checked by a second microscopist. Because discrepancies were noted in two subjects, all blood smears were read by a third qualified microscopist. To search for adverse effects, thorough examinations were done on each visit. Signs and symptoms were recorded on a standard form. All case report forms were reviewed daily. Adverse effects were defined as signs and symptoms that first occurred or became more severe after treatment started.

Criteria of therapeutic response were early treatment failure, late treatment failure and adequate clinical response as defined by WHO (1996) protocol (Table I). Informed consent for participation was obtained from patients and/or from the legal guardians of minors. Ethical clearance was provided by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Bordeaux, France (N° 2002/24 from the 27/03/02).

## RESULTS AND DISCUSSION

Of the 2500 all mixed attended patients, 55 had a positive dipstick and parasitaemia. Two persons were excluded (one adult for cholecystitis, and a 12 years old child for his signs were judged serious) and referred to Mayotte hospital. Fifty-three persons (42 M / 11 F) were enrolled in the study. One person was lost to follow-up for missing the third AL dose on day 1. One patient 18 years aged (with negative blood smear from day 3 to 21) was withdrawn on day 13 for developing a serious adverse event due to viral meningo-encephalitis, which might have

## Criterion

**Early treatment failure** (one of the following conditions from day 0 to day 3)

Development of danger signs or severe malaria on day 1, day 2 or day 3, in the presence of parasitaemia;  
 Axillary temperature  $\geq 37.5^\circ\text{C}$  on day 2 with parasitaemia  $>$  of day 0 count;  
 Axillary temperature  $\geq 37.5^\circ\text{C}$  on day 3 in the presence of parasitaemia;  
 Parasitaemia on day 3  $\geq 25\%$  of count on day 0.

**Late treatment failure** (one of the following conditions from day 4 to day 14)

Development of danger signs or severe malaria in the presence of parasitaemia on any day from day 4 to day 14, without previously meeting any of the criteria of early treatment failure  
 Axillary temperature  $\geq 37.5^\circ\text{C}$  in the presence of parasitaemia on any day from day 4 to day 14, without previously meeting any of the criteria of early treatment failure.

**Adequat clinical response** (one of the following conditions up to day 14)

Absence of parasitaemia on day 14 irrespective of axillary temperature, without previously meeting any of the criteria of early or late treatment failure;  
 Axillary temperature  $< 37.5^\circ\text{C}$  irrespective of the presence of parasitaemia, without previously meeting any of the criteria of early or late treatment failure.

Table I. – WHO classification of therapeutic response, 1996.

nothing to do with the treatment itself (after five days of hospitalization, the patient totally recovered with no after-effects). Finally, the whole data set consists of 51 patients.

On admission, the mean age and weight ( $\pm$  standard deviation) were 18.7 ( $\pm 10.2$ ) years and 45.6 ( $\pm 16.2$ ) kg; six patients (12%) were children under five. Mean axillary temperature was  $38.6^\circ\text{C}$ , mean glycemia was 0.97 g/liter, mean hemoglobin was 12.1 ( $\pm 1.8$ ) g/dl, and mean parasitaemia was 30,820 asexual parasites/ml of blood (Table II). At enrollment, four children and one adult presented with a hemoglobin rate between 5 and 7 g/dl. These were controlled the following days to ensure that normal levels were restored. Four individuals (7.2 %) have spent the month preceding the study in the neighboring islands of the Comoros Union. The AL combination was safe as shown by hematocrite values on days 0 and 3. One case of post therapeutic pruritus occurred with an adult.

None of the included cases progressed to severe malaria. No therapeutic failure, either early or late was observed. After 24 h's treatment, 14 patients (26.9 %) were still febrile and only two ones still had parasites (3.8 %). After 48 h's treatment, all patients were afebrile and none of them had parasitemia until the end of the 21 day follow-up period.

This study showed that the AL combination is clinical and parasitological responsive in treatment of uncomplicated falciparum malaria in Mayotte Island. This treatment resulted in excellent parasite clearance, acted rapidly, resolved the symptoms and was well tolerated, as reported in other studies (van Vugt *et al.*, 1999; Kshirsagar *et al.*, 2000; van Agtmael *et al.*, 1999; Hatz *et al.*, 1998).

The combination therapy is a strategy in malaria control that has received much attention recently in multi-drug resistant areas (White *et al.*, 1999). AL combination is a rapidly active artemisinin derivative with a longer acting antimalarial drug. In high transmission area, the treatment therapy of four dosages gave satisfactory results. However, in non-immune populations, in South-Eastern Asia, the four dosage therapy knew 20 % of failure, reduced to 5 % when the dosage was increased to six (van Vugt *et al.*, 1998; Looareesuwan *et al.*, 1999). In lack of sufficient data, AL is not recommended on pregnant or breast feeding women or on less than 10 kg child either. But, in addition to the efficacy, the easy to take presentation, the availability in the market, the non cardiotoxicity (van Vugt *et al.*, 1999) contribute to its good position in combined treatments.

		day 0	day 1	day 2	day 3
Parasitaemia (trophozoites/ $\mu\text{l}$ )	mean (SD)	30,820 (44,537)	280 (1,496)	0	0
Axillary temperature ( $^\circ\text{C}$ )	mean (SD)	38.6 (1.2)	37.1 (1.1)	36.5 (0.5)	36.5 (0.2)
	maximum	40.6	40.2	37.6	37.3
Hemoglobin (g/dl)	mean (SD)	12.1 (1.8)	Not done	Not done	12.4 (1.2)
	minimum	6.9			7.3
Glycemia (g/l)	mean (SD)	0.97 (0.2)	Not done	Not done	1.0 (0.3)
	minimum	0.67			0.72

Table II. – Baseline characteristics of the 51 patients at enrolment for malaria attack, Mayotte, April-May, 2002.

Beyond the particular interest of the malaria control health authorities in Mayotte, this study on the AL four dosages efficacy contributes to the thought on a strategy based on combined treatments in the sub region of the Indian Ocean including all the islands of the Comoros Archipelago. It will help also to preserve the north-western coast of Madagascar (which is the critical area of entry) against the invasion of resistant strains coming from the Comoros Archipelago.

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